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Pesticide Fact Sheet Number 231: Prodiamine

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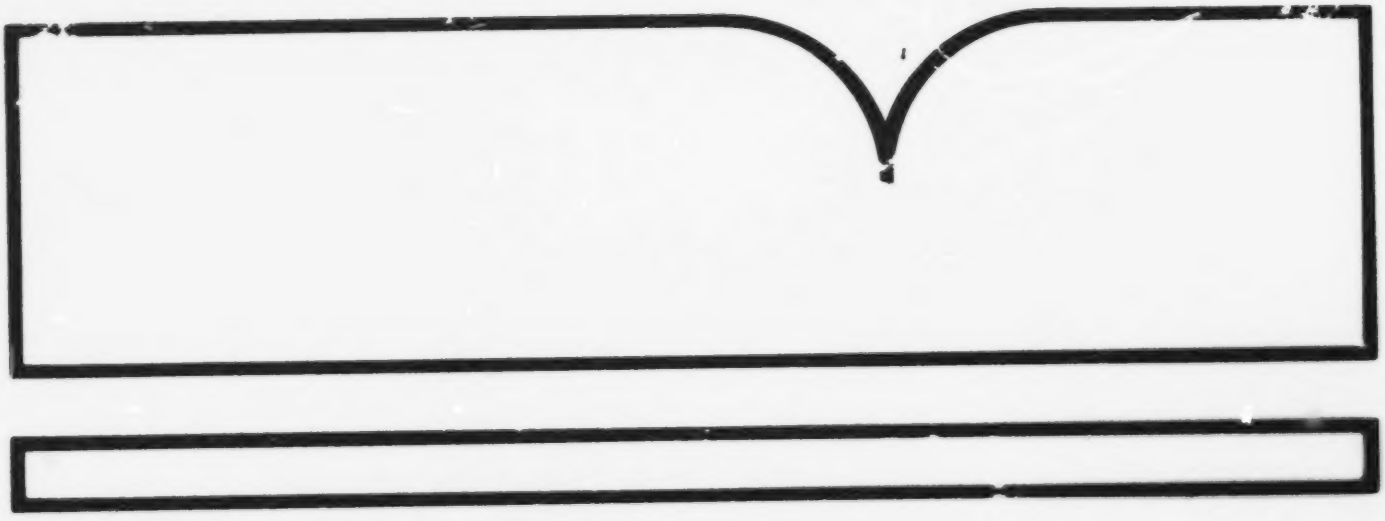

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This document contains up-to-date chemical information, including a summary of the Agency's regulatory position and rationale, on a specific pesticide or group of pesticides. A Fact Sheet is issued after one of the following actions has occurred.

1. Issuance or reissuance of a registration standard,
2. Issuance of each special review document,
3. Registration of a significantly changed use pattern,
4. Registration of a new chemical, or
5. An immediate need for information to resolve controversial issues relating to a specific chemical or use pattern.

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b. Identifiers/Open-Ended Terms

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EPA

Pesticide Fact Sheet

540/FS-92-175

PB92-145416

Name of Chemical: Prodiamine
Reason for Issuance: Registration
Date Issued: 2/7/92
Fact Sheet Number: 231

1. DESCRIPTION OF CHEMICAL

Generic Name: N^3,N^3-Di-n-propyl-2,4-dinitro-6-(trifluoromethyl)-m-phenylenediamine
Common Name: Prodiamine
Trade Names: Barricade®
EPA Shaughnessy Code: 110201
Chemical Abstracts Service (CAS) Number: 29091-21-2
Year of Initial Registration: 1991
Pesticide Type: Herbicide
Chemical Family: Dinitro-aniline
U.S. Producer: Sandoz Crop Protection Corporation

2. USE PATTERNS AND FORMULATIONS

Application sites: Terrestrial non-food sites. Preemergence for selective control of annual grasses and broadleaf weeds in established lawns and in landscape ornamentals.

Types of formulations: The two end-use products are water disperseable granular formulations of the active ingredient; with a nominal concentration of 65.0% of the active ingredient. One product is packaged in water soluble bags to reduce applicator exposure associated with handling and applying the product.

Amount and Method of Application: Application rates for 2-6 months control of weeds varies between 0.325 and 1.5 lbs. of active ingredient per acre, depending on the weeds to be controlled. Maximum annual application rates varies between 0.5 and 1.5 lbs. of active ingredient per acre, per season; depending on the species of turf grass. Ground spray application of aqueous suspensions of the formulated product is the only method of application registered.

Carrier: Water

3. SCIENCE FINDINGS

Summary Science Statements:

Adequate toxicological, product chemistry, ecological effects, environmental fate and ground water data have been submitted and reviewed to support the conditional registration of prodiamine for use as a preemergence herbicide in the culture of ornamental turf grasses and landscape ornamentals. Technical prodiamine is classified as a Toxicity Category III pesticide and is labeled with the signal word "CAUTION", based on a battery of 6 acute studies.

Studies demonstrated that prodiamine generally has a negative mutagenic activity. However, there was a suggestive activity in Salmonella strain TA 1538 without activation (Registrant claimed that material tested was from an outdated manufacturing process) and in mouse lymphoma cells without activation, but negative in confirmatory testing. Prodiamine was not a developmental toxicant. In a rat teratology study the developmental toxicity NOEL was 300 mg/kg and the LEL was 1,000 mg/kg based on the total number of fetuses/litter with malformations. The maternal toxicity NOEL was 300 mg/kg and the LEL was 1,000 mg/kg based on depressed body weight gain. In a rabbit teratology study there was no evidence of developmental toxicity at 500 mg/kg/day the highest dose tested (HDT). A two gereration reproduction study in rats demonstrated a reproductive toxicity NOEL of 200 ppm based on reduced pup weight and increased relative liver weight at 2000 ppm.

In a rat carcinogenicity study prodiamine at 3200 ppm in the diet increased thyroid follicular cell neoplasia in in both sexes. Positive dose-trends in thyroid follicular cell adenomas and in combined follicular cell tumors (adenomas and carcinomas) in both males and females were observed. In addition, a statistically significant positive trend in incidence of pancreatic adenomas was observed in female rats; although the dose trend for the incidence of carcinomoas and adenomas (combined) was not significant.

In a mouse carcinogenicity study with prodiamine there was found an increase in subcutaneous fibrosarcomas in high level male mice related to fighting.

Based on a "weight-of-evidence" analysis, prodiamine was determined to be a Group C carcinogen. EPA Health Effects Division's Peer Review Committee recommended that a Reference Dose Approach should be used for quantification of risk to humans.

Prodiamine appears to be metabolized rapidly by dealkylation reactions to N,N-didespropyl metabolites. Cyclization also occurs to form N-propyl benzimidazole A and N-propyl benzimidazole B found in feces. The N-propyl benzimidazoles were metabolized further via nitro-reduction, N-dealkylation, and ring hydroxylation to form hydroxy-benzimidazoles found in urine.

Acute toxicology studies with technical prodiamine and the two end-use products containing 65.0% active prodiamine demonstrated that prodiamine is of low acute toxicity to mammals.

A 13-week subchronic feeding study in rats demonstrated that the lowest effect level in rats was 4000 ppm. The effect was reduced body weight gain, increased cholesterol and increased urinary protein content.

Prodiamine is very water-insoluble and is not hydrolyzable. Absorption, leaching and run-off studies indicate that movement in soil is unlikely. Volatility is not significant. Prodiamine is stable to hydrolysis and moderately bound to sediment. Data demonstrate that prodiamine is rapidly degraded in water exposed to natural sunlight.

An avian single dose oral LD_{50} study with bobwhite quail demonstrated that prodiamine is accutely non-toxic to bobwhite quail. The no-observed-effect dosage was > 2250 mg/kg/day. In eight day dietary studies with mallard duck and bobwhite quail the LC_{50} level was > 10,000 mg/kg/day, the highest concentration fed.

Prodiamine is not expected to pose a significant acute hazard to freshwater organisms at its limit of solubility in water (13 ppb).

Chemical analysis of both the manufacturing-use and the end-use products demonstrated that nitrosoamine would not be expected to be present in these products at levels of toxicological concern.

Chemical Characteristics:

Physical State:	Solid, powered
Color: Chemically Pure:	Yellow-orange
Technical Grade:	Yellow-orange
Odor:	Halide odor
Melting Point:	122.5-124.0°C
Density:	1.4107 gm/ml (typical)
Molecular Weight	350.3
Empirical Formula	$C_{13}H_{17}F_3N_4O_4$

Solubility	Solvent		at °C
Parts per Million:	Water	0.013	25° C
Grams per 100 ml:	Acetone	22.600	25° C
	n-octanol	0.962	25° C
	Dimetnyl formamide	32.100	20° C
	Xylene	3.540	20° C
	Isopropanol	0.852	20° C
	Heptane	0.100	20° C

Vapor Pressure: 2.5×10^{-8} mm/Hg at 25°C

Dissociation Constant: Data waived because of low water solubility.

Octanol/Water Partition Coefficient: $P = 1.3 \times 10^4$

pH: (in non-aqueous solvent): 6.878 at 25°C

Stability: Thermally stable. Moderately stable to light. Decomposes at 240°C

Oxidizing or Reducing Action: Slight oxidizing potential

Explodability: Non-explosive

Storage Stability: Stable for 84 days at 54°C and 168 days at 40°, and 1 year at ambient temperature

Toxicology Characteristics:

Acute Toxicity (93.0%, Technical)

Acute oral toxicity in rats: LD_{50} > 5000 mg/kg (M&F)
Toxicity Category IV.

Acute dermal toxicity (rat): LD_{50} > 2,000 mg/kg (M&F)
Toxicity Category III.

Primary dermal irritation (rabbit): Non-irritating to skin of rabbits
Toxicity Category IV.

Primary eye irritation (rabbit): No corneal opacity; minimally irritating to eyes of rabbits
Toxicity Category III.

Acute inhalation toxicity (rat): LC_{50} > 0.256 mg/m^3 for males and females
Toxicity Category III.

Dermal sensitization (guinea pig): Not a dermal sensitizer.

Acute Toxicity for Barracade® 65 WDG Herbicide

Acute oral toxicity (rats): LD_{50} > 5000 mg/kg (M&F)
Toxicity Category IV.

Acute dermal toxicity (rats): No deaths, LD_{50} >2000 mg/kg, Category III.

Primary dermal irritation (rabbit): Very slight erytheme in 1 of 6 rabbits
Category IV.

Primary eye irritation (rabbit): 5/6 rabbits had conjunctival redness and chemosis > score 1, but reaction vanished by 4th day.
Category III.

Acute inhalation toxicity (rat): LC_{50} > 1.81 mg/L (M&F)
Category III.

Dermal sensitization (guinea pig): Positive for dermal sensitization.

Subchronic and Chronic Toxicity

A 13-week feeding study with rats demonstrated a no observed effect level (NOEL) of 1200 ppm; a least effect level (LEL) of 4000 ppm. The observed effects seen in both male and females were a reduction of body weight gain and increased cholesterol value. Increased urinary protein content was seen only in males.

In a rat developmental toxicity study developmental effects (increased incidence of omphalocele) were observed only at 300 mg/kg (LEL). The NOEL for this developmental effect was 100 mg/kg. A maternal effect (depressed body weight gains) was also observed at at 1000 mg/kg (LEL). The NOEL for this effect was 300 mg/kg.

In a rabbit developmental toxicity study there were no developmental effects at 500 mg/kg/day (HDT). A maternal effect (reduced body weight gain) was observed at 300 mg/kg (LEL) The NOEL for this effect was 100 mg/kg/day.

A 2-generation reproduction study in the rat treated with 0, 50, 200, and 2,000 ppm prodiamine had a NOEL of 200 ppm (approximately 10 mg/Kg/day) based on reduced pup weight and increased relative liver weight at 2,000 ppm.

Mutagenicity

The following mutagenicity studies indicated that prodiamine is not generally mutagenic at doses tested:

- Ames Assays for mutagenicity with TA1538 strain of Salmonella were found positive for increased revertants in TA1538 at 5000 ug/plate in the absence of activation. The registrant states that the material tested was from an outdated manufacturing process.

- Ames Assays for mutagenicity with five tester strains of Salmonella were negative for reverse gene mutation (his^- to his^+) at 10,000 ug/plate with or without metabolic activation up to 10,000 ug/plate with precipitation at 500 ug/plate and above.

- Ames Assays for mutagenicity with Salmonella was negative at 0.3 - 100 ug/plate with or without metabolic activation.

- A mutagenic-unscheduled DNA synthesis study demonstrated that prodiamine was non-mutagenic.

- Mouse lymphoma foreward mutation assay with or without metabolic activation at concentrations of 0.5, 1, 4, 6, 8, 10, 13. 16. 20, and 50 ug/ml with activation was negative. In a nonactivated study it was also negative at 1, 10, 40, 60, 80, 100, 130, 160, 200 and 500 ug/mg.

A 2-year feeding/oncogenic mouse study demonstrated a significant increased incidence of subcutaneous fibrosarcoma in high dose males was related to fighting activity caused by group caging. Levels tested were 0, 50, 500, and 5000 ppm (M: 0, 6.2, 59.4 and 606.6 mg/kg/day; F: 0, 6.8, 64.6 and 646.2 mg/kg/day). Systemic effects (reduced body weight gains and increased liver weight) were observed at 5000 ppm (LEL). The NOEL for this effect was 500 ppm.

A 2-year feeding/oncogenic rat study demonstrated a significant increased incidence of follicular adenoma/carcinoma in both males and females. Levels tested were 0, 50, 200, 800 and 3200 ppm (M: 0, 1.8, 7.2 29.4, and 115.2 mg/kg/day; F: 0, 2.3 9.1, 37 and 151 mg/kg/day). Systemic effects (increased liver weight and minor biochemical disturbances) occurred at 800 ppm (LEL). The NOEL for this effect was 200 ppm.

In a metabolism study with rats, prodiamine was absorbed and readily eliminated after a single dose of 10 or 400 mg/kg of C^{14}-prodiamine or a single oral dose of 10 mg/kg of the radioactive compound following 14 days of administration of 10 mg unlabeled prodiamine/kg/day. All but high-dose female rats had eliminated about 70% of the C^{14} dose in the urine and feces within 24 hour (high-dose females excreted about 38% of the dose). Tissue radioactivity levels were slightly higher in females than those in males. C^{14} prodiamine and its metabolites did not accumulate in the body to an appreciable extent.

Mechanism of Pesticidal Action:

Prodiamine is a mitotic inhibitor of normal cell division of susceptible plants. The formation and function of microtubulin is inhibited. Susceptible plant roots are stunted and fail to function in the presence of prodiamine. Plants do not grow and develop through their normal cycle of vegetative growth followed by reproduction (flowering and seed setting). Susceptible plants react to prodiamine in such a way as to be less competitive.

Environmental Characteristics:

Hydrolysis: Prodiamine slowly hydrolyzes in the pH range of 5-9. No significant degradation occurs after 30 days. A hydrolysis study conducted at pH 5, 7 and 9 indicated that degradation by hydrolysis is greater than 6 months.

Photodegradation: The half-life of prodiamine is 20 minutes in deionized water and 40 minutes in natural water.

Aerobic Soil Metabolism: The anerobic breakdown of prodiamine in soil is considerably more rapid than aerobic breakdown. Different metabolites were observed for these conditions of metabolism. The bound residue level was higher under anaerobic conditions. Prodiamine had a half-life of 34 days under anerobic conditions and 218 days under aerobic conditions. The half-life of prodiamine under aerobic soil conditions is approximately 2 months. The major soil degradate is 6-amino-benzimidazole under aerobic soil conditions.

Leaching: Prodiamine or its degradates do not leach significantly. Under field conditions prodiamine is immobile with regard to downward movement in soil.

Runoff: Runoff of prodiamine is unlikely to occur because of its insolubility and immobility.

Soil Adsorption/ Desorption: Prodiamine is very strongly adsorbed to soil, more strongly than dinitramine. Data demonstrate that prodiamine is extremely immobile.

Potential to Contaminate Ground Water: The low solubility in water and its high tendency to bind to soil prevents prodiamine from being carried downward through soil. Prodiamine has a low potential for leaching into ground water. Surface water contamination from soil containing prodiamine would be expected.

Ecological Characteristics

Avian Studies: Prodiamine is practically non-toxic to birds based on the following studies:

Single Dose Acute Oral LD_{50}:
Bobwhite Quail with 96.3% Technical:
LD_{50} > 2250 mg/Kg

Eight Day Dietary Study:
Mallard duck with 98.4 Technical:
LC_{50} > 10,000 ppm
Bobwhite quail with 98.4% Technical:
LC_{50} > 10,000 ppm

Avian Reproduction: A study is required as a condition for registration.

Aquatic Organisms: The following data indicate that prodiamine is not toxic to freshwater fish and aquatic invertebrates:

Fish Acute Toxicity:
Bluegill sunfish, LC_{50} > 552.0 ppb
Rainbow trout, LC_{50} > 829.0 ppb

Freshwater Invertebrates:
A 48-hour EC_{50} in Daphnia was > 658 ppb

Honey Bee:
Acute contact LD_{50} > 100 ug/bee.

Endangered Species Hazards:

Based on available data, the conditionally registered use-pattern of prodiamine is unlikely to pose a hazard to endangered aquatic and avian species. There may be some hazard to endangered plant species from runoff and movement of the products from treated turf areas.

4. Summary of Regulatory Postion and Rationale

Available data provide adequate information to support the conditional registration of Barricade® T Herbicide, Barricade 65 WG Herbicide, and Barricade 65 WG Herbicide in Water Soluble Packs, that were first conditionally registered February 7, 1992 under Section 3 of the Federal Insecticide, Fungicide and Rodenticide Act as amended.

Use, Formulation, Manufacturing Process or Geographic Restrictions:

- o Aerial applications of prodiamine products are not permitted. Probition against aerial applications must appear on labeling.
- o End-use products must bear the following precautions:
  "May cause an allergic skin reaction. Wash thoroughly with soap and water after handling."
  "During mixing and loading wear chemical resistant gloves. Wash non-disposable gloves thoroughly with soap and water before removing. Remove contaminated clothing and separately launder clothing before use.

Conditional registration will expire on February 1, 1995.

5. Summary of Data Requirements

Toxicology Data:

1. Acute and 90-day neurotoxicity screening Battery in rats (EPA Guideline Numbers 81-8 and 82-7). Data are due February 1, 1994.

3. Study in rats to measure effects on TSH, T_3 and T_4. Data are due April 1, 1993.

Exposure Data:

1. Worker Exposure Studies. Reserved pending review of required toxicology data listed above.

2. Reentry data: Subpart K (Foliar Dissipation (132-1), Soil Dissipation (132-2), Dermal Exposure (132-3), and Inhalation Exposure (132-4)). Reserved pending review of required toxicology data listed above.

Ecological Effects Data:

1. Avian Reproduction with a Waterfowl and Bobwhite Quail, EPA Ref. Guidelines 71-4. Data are due May 1, 1994.

2. Acute LC_{50} Estuarine/Marine Organisms Studies, EPA Ref. Guidelines 72-3, identified as:
   - o 96-hour LC_{50} for an estuarine marine fish
   - o 96-hour LC_{50} for a shrimp species
   - o Either a 48-hour embryo larvae study or a 96-hour shell deposition study with oyster.

   Data are due February 1, 1993.

3. Fish Early Life Stage and Aquatic Invertebrate Life-Cycle Studies, EPA Ref. Guidelines 72-4. Data are due May 1, 1993.

4. Target Area: Phytotoxicity (if end-use product is aerially applied).

   Tier II:
   - o Seed Germination/Seedling Emergence, 10 species, EPA Ref. Guideline 123-1
   - o Vegetative vigor, 10 species, EPA Ref. Guideline 123-1
   - o Aquatic plant growth (5 species), EPA Ref. Guidelines 123-2

   Tier III:
   - o Terrestrial Field[1], EPA Ref. Guidelines 124-1
   - o Aquatic field[2], EPA Ref. Guidelines 124-2

   1/ Required if a 25 percent or greater detrimental effect was found in 1 or more plant species in corresponding test of previous tier.

   2/ Required if a 25 percent or greater detrimental effect was found on any plant species in the corresponding test of the previous tier.

   Data are due at the time of application to amend any registration of prodiamine to allow aerial application.

Environmental Fate and Ground Water Data:

1. Prodiamine Aged-Leaching Study, EPA Ref. Guidelines 163-1. Data are due June 31, 1992.

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